EFFICACY OF ORAL WATER SOLUBLE VITAMIN-K IN NEONATES

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DOCTOR OF MEDICINE
(PAEDIATRICS)

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C E R T I F I C A T E

This is to certify that the work entitled "EFFICACY OF ORAL WATER SOLUBLE VITAMIN 'K' IN NEONATES" has been carried out by OM PRAKASH YADAV in the department of Paediatrics, M.L.B. Medical College, Hospital, Jhansi.

He has put in the necessary stay in the department as per university regulations.

Dated: 11.10.91

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C E R T I F I C A T E

This is to certify that the work entitled "EFFICACY OF ORAL WATER SOLUBLE VITAMIN 'K' IN NEONATES" which is being submitted as thesis for M.D. (Paediatrics) examination, 1992 by OM PRAKASH YADAV, has been carried out under my direct supervision and guidance. The techniques embodied in the thesis were undertaken by the candidate himself and the observations recorded have been regularly checked by me.

Dated: 11.10.91

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Dated: 11-10-91

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A C K N O W L E D G E M E N T

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Without any stringe attatched it can be said with sureness that the timely completion of this work is not wholly but completely due to keen personalized interest precise guidance and step by step help received from you Sir.

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Dated: 11/10/1991

(OM PRAKASH YADAV)

C O N T E N T S

INTRODUCTION

INTRODUCTION

Haemorrhagic disease of the newborn (HDN) has been a well recognised entity. The term haemorrhagic disease of the newborn (HDN) was first used in 1894 when Townsend reported 50 infants with bleeding during the first two weeks of life.

By 1950, haemorrhagic disease of the newborn seemed fairly well understood. It caused spontaneous bleeding in the first few days of life (typically in breast fed infants) and was associated with a clotting defect that was rapidly corrected by the administration of vitamin K.

Lane and Hathway (1985) in a recent review described three types of hemorrhagic diseases - early that occurs in compromised babies and babies whose mothers have been on anticonvulsants, disease that occurs on 2nd to 5th day of life (classic HDN) and late hemorrhagic disease that occurs upto six weeks of life. All these three types of HDN are preventable with vitamin K prophylaxis.

Breast milk is deficient in vitamin K and causes late colonization of gut and thus plays an important role in the pathogenesis of HDN. Breast feeding has been implicated as a necessary factor in the pathogenesis of hemorrhagic disease of the newborn (Sutherland

et al, 1967). Vitamin K is approximately four times more concentrated in cow's milk than in breast milk (Dam et al, 1942) and clotting factors dependent on this vitamin are decreased in normal term infants, and even more reduced in premature infants(Bleyer et al, 1971 and Hathway, 1975).

A national survey of HDN in Japan showed an incidence of 1:4500 in unselected cases and 1:1700 among breast fed infants (Hanawa et al, 1988). The recent world-wide increase in the incidence of HDN is believed to be due to the resurgence of breast feeding.

Although there is no unanimity over the absorption of oral vitamin K, McNinch et al and Sann et al(1985) claimed 29% absorption from an oral dose of vitamin K. Exclusively breast fed babies have prolonged prothrombin time (Keenan et al, 1971) and as a result 15-20 times greater risk of bleeding (Lane and Hathway, 1985), as compared to those given cow's milk, vitamin K or both. Among full term infants the incidence of haemorrhagic disease of the newborn has ranged from 0.25- 1.75% (Sutherland et al, 1967).

Tripp and McNinch in 1987 in their annotation said "While admitting the wide gaps in our knowledge of HDN, two facts are undisputed, firstly, the condition is virtually confined to breast fed infants who are not given vitamin prophylaxis. Secondly, it carries a high risk of morbidity or death. Now that it is again common for

babies to be solely breast fed, even to the exclusion of supplementary formula feeds while breast feeding is becoming established, we strongly recommended that all, infants should receive vitamin K prophylaxis.

Though most authorities recommend routine intramuscular vitamin K prophylaxis, it is not universally followed. With the increasing emphasis on exclusive breast feeding the worldover including India, it is justifiable to fear that the incidence of hemorrhagic disease may increase unless adequate vitamin K prophylaxis is provided.

Yellis (1941) said "Despite all the arguments and counter arguments of the past we believe that weights of evidence clearly indicates the benefits to be derived from the routine administration of vitamin K to all newborn infants. There seems to be no justification what-so-ever for withholding this preparation and we would earnestly hope that the subject will not be reopened for at least 10 years; even 20 years would be better.

In this study, we evaluated the efficacy of an oral water soluble vitamin K preparation (Menadione sodium bisulphite) and compared it with efficacy of parenteral vitamin K.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Haemorrhagic disease of the newborn (HDN) is a serious haemorrhagic disorder associated with vitamin 'K' deficiency, most commonly seen in breast fed babies.

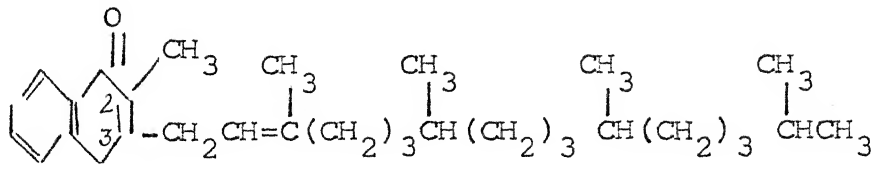
The term haemorrhagic disease of newborn was first used in 1894 when Townsend reported 50 cases (infants) of bleeding disorder in whom the bleeding had occurred within the first two weeks of life. He observed that the haemorrhage generally began on the 2nd or 3rd day of postnatal life. He also differentiated this acquired haemorrhagic disease from inherited haemophilia.

Vitamin 'K' was not discovered until 1929 when Dam observed bleeding in chickens, fed on fat free diet (Diet free from ether soluble components). Thus "historically, vitamin 'K' (Koagulation vitamin) acquired its name with the discovery that chickens fed on fat free diet bled to death". Since then vitamin 'K' has been isolated in 3-main forms.

Vitamin 'K' is a naphthoquinone derivative and is related to 2-methyl-1, 4-naphthoquinone.

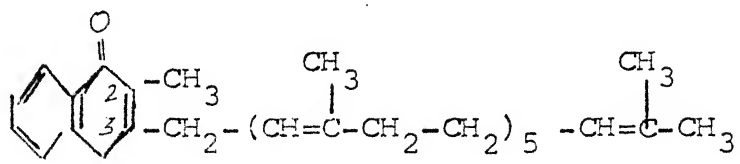
1. First form is vitamin 'K_1' : It is a naturally occurring fat soluble, vitamin 'K' found in dark green leafy vegetables, such as spinach, cabbage etc. It possesses phytyl radical at position 3. Vitamin

K_1 is also termed as phytonadione or phylloquinone or mephyton.



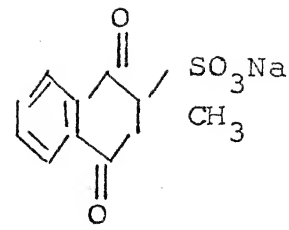
Vitamin 'K_1' : Phytonadione (Phylloquinone; Mephyton).
(2-methyl-3 phytyl-1, 4-naphthoquinone).

2. Second form is vitamin 'K_2' : It is synthesized by intestinal bacterial flora. It has difarnesyl radical at position 3. Vitamin K_2 is also termed as farnoquinone or Menaquinone.

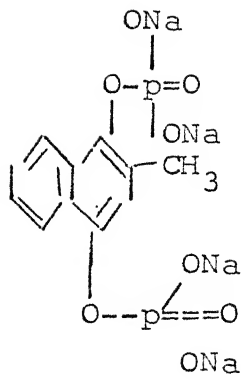


Vitamin K_2 : Farnoquinone; Menaquinone
(2-methyl-3-difarnesyl-1, 4-naphthoquinone).

3. Third form is vitamin 'K_3' : It is a synthetic form and water soluble. It is termed as Menadione. It is found in two main forms. First form has a phosphate radical in it and is known as synkayvite. The second form has a sulfate radical in place of phosphate radical and is known as hykinone.



Hykinone (Menadione - sodium disulfite).



Synkayvite (sodium menadione diphosphate).

MERITS AND DEMERITS OF VARIOUS FORMS OF VITAMIN 'K'

1. Naturally occurring vitamin K i.e. vitamin K_1 causes hyperbilirubinaemia in premature and compromised infants.
2. Synthetic preparations of vitamin K i.e. vitamin K_3 causes hyperbilirubinaemia to a lesser extent than vitamin K_1 : but it causes hyperbilirubinaemia in those infants who are deficient in G-6 phosphate dehydrogenase enzyme.
3. It has been postulated that synthetic preparation of vitamin 'K_1' (konakione) which can be used orally or parenterally does not cause hyperbilirubinemia of any significance even in G-6 phosphate dehydrogenase deficient infants and, thus, it may be recommended by both routes in doses of 1 mg.

SOURCES AND ABSORPTION OF VITAMIN 'K' IN INFANCY

Sanford et al (1932) observed that diet was an important source of vitamin 'K' immediately after birth. They further suggested that early supplemental feedings could reduce the incidence of haemorrhage during the first week of life.

Aballi et al (1966) claimed that absorption of vitamin 'K' from the colon of human neonate was good but the relative importance of intestinal flora in providing vitamin 'K' to the infant was unknown.

Frick et al (1967) observed, in their study of 10 adults, that ⊠total starvation combined with antibiotic administration did not induce vitamin 'K' deficiency until 21 to 28 days had elapsed.

Shearer et al (1970) documented that in a vitamin 'K' replete man the radio activity persisted in the plasma for 3-4 days after the ingestion of tritiated vitamin 'K_1'.

Keenan et al (1971) documented that flora of breast fed infants could produce less vitamin 'K' than the flora or formula fed infants.

Many bacteria, including normal intestinal flora, are capable of synthesizing quinones with vitamin 'K' activity. Cow's milk has more vitamin 'K' than human milk. According to Harper (1977) deficiency of vitamin 'K_2' occurs as a result of prolonged therapy

with sulfaguanidine, succinyl sulfathiazole or salicylate, all capable of suppressive bacterial flora which synthesize vitamin 'K_2'.

Bjornsson et al (1980) observed that vitamin K storage in human infant was not known but higher molecular weight storage forms of vitamin K could exist.

Corrigan (1981) observed that fat soluble vitamin 'K_1' or phylloquinone was the principal form of vitamin 'K' in plants and vegetable oils and required bile acids for its absorption from small intestine. Author also documented that the vitamin 'K' was not stored in human infants to any significant degree. But according to Hollander (1981) in animals the absorption of vitamin 'K_1' across the intestinal mucosa was energy dependent transport.

According to Harron et al (1982), most of the commercial formulae in the United States contain more than 50 micro gm/l of vitamin K_1. In contrast, vitamin K content in human milk varies widely, but was generally $\angle$20 micro gm/l and often below 5 micro gm/l.

Bentley and Meganathan (1982) documented that vitamin 'K' was synthesized by intestinal mucosa in the form of fat soluble menaquinone or vitamin 'K_2'. Authors further documented that the bacteria differed widely in this in their ability to synthesize vitamin K_2. Bacteroids fragilis and some strains of E. Coli were

efficient producers of vitamin K_2, whereas some lactobacilli and pseudomonas organisms were incapable of its synthesis.

Sann et al (1983) observed that oral administration of vitamin K_1 was effective in maintaining significant serum level of vitamin 'K' for at least 5 days.

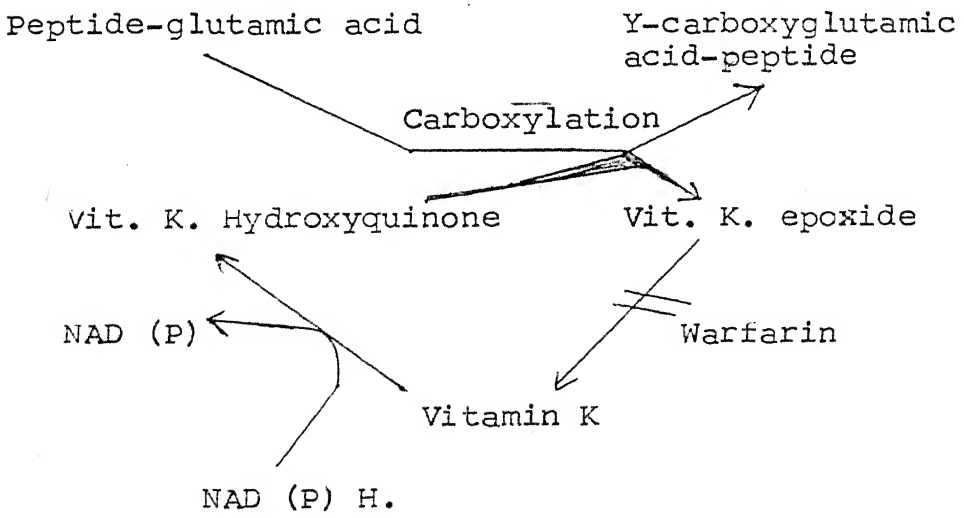
According to Barness (1987) naturally occurring vitamin 'K' is fat soluble and is found in high concentration in hog's liver, soybeans and alfalfa and in smaller amounts in some vegetables such as spinach, tomatoes, Kale etc. This vitamin was labelled vitamin K_1 to distinguish it from synthetic naphthoquinones with vitamin K like activity.

BIOLOGIC FUNCTIONS OF VITAMIN 'K'

Stenflo et al (1974) wrote"the specific action of vitamin K was post-translational carboxylation of glutamic acid residues on (unless it is quoted) vitamin K dependent proteins". This conversion of glutamic acid to Y carboxyglutamic acid creates effective calcium binding sites on these proteins. Noncarboxylated proteins are functionally defective because they cannot bind calcium e.g. prothrombin requires calcium for its activation to thrombin, which in turn converts fibrinogen to fibrin.

Corrigan (1981) observed that oxidative phosphorylation of glutamic acid was due to vitamin K. Synthesis of factor II, factor VII, Factor IX and factor X were dependent on vitamin 'K'. Author further suggested that protein C was vitamin K dependent and when activated inhibited coagulation function of factor VIII and factor V and stimulated fibrinolysis. Author also reported that vitamin K dependent calcium binding proteins such as osteocalcin promoted phospholipid interaction in coagulation and in calcium binding metabolism.

Gallop et al (1980), Uotilla and Suttie(1982), and Leibman et al (1982) documented that the vitamin K dependent carboxylation of coagulation factors occurred in the rough endoplasmic reticulum of the hepatocytes.



Courtsey - Gallop et al, Uotilla and Sittie, and Leibman et al.

Vitamin K : Hydroxyquinone _ active form of vit. K.

EFFECT OF EXCESS OF VITAMIN 'K' IN NEWBORNS

Barness (1987) documented that effects of excess vitamin K were still not established and claimed that it could produce hyperbilirubinaemia in premature newborn infants if given in higher doses.

MORTALITY AND MORBIDITY OF VITAMIN 'K' DEFICIENCY HAEMORRHAGE(S)

Dam (1894) reported 50 cases of bleeding which occurred during the first 2 weeks of life, and differentiated it from inherited hemophilia. Stuart (1977) in his study observed that the transient deficiency of vitamin K dependent factors was probably due to lack of free vitamin K in mothers, immaturity of infant's liver and the absence of intestinal bacterial flora (normally responsible for the synthesis of vitamin K). Author further observed that rarely, among the term infants and more frequently among premature infants, there was an accentuation and prolongation of this deficiency between the 2nd and 5th days of life, resulting in spontaneous and prolonged bleeding.

Nakayama et al (1981) reported 425 infants of bleeding disorder due to late onset of vitamin K deficiency.

McNinch et al (1983) reported six cases (6 in 1200 LIVE births) of haemorrhagic disease in a single district, in his 17 month's study period. But, those [illegible] were breast fed and none had received vitamin

K at birth.

Martin et al (1983) reported 741 cases of vitamin K deficiency haemorrhage in Vietnam. These cases also included 171 deaths which were traced to the use of warfarin contaminated milk powder.

Lane et al (1983) reported a fatal case of vitamin K deficiency in an otherwise healthy 1-month old child who had not received vitamin K prophylaxis at birth.

Chaou et al (1984) reported intracranial haemorrhage, proved by CT scan, in 32 breast fed babies and traced the relation of their disorder to reduced availability of vitamin K. Further, in a 2 year follow up study of the same, they reported that only one showed normal development while all others developed microcephaly and some degree of handicap.

Sutor et al (1985) from West Germany reported 20 cases over a period of 4 years, suggesting an incidence of 1 per 100,000.

Motohara et al (1987) documented that the level of acarboxyprothrombin (PIVKA-II) was higher in breast fed babies than formula fed babies.

Lane et al (1985) documented that haemorrhagic disease of the newborn (HDN) had an approximate incidence of 1 per 1000 live births.

CLINICAL MANIFESTATIONS OF VITAMIN 'K' DEFICIENCY

Three patterns of haemorrhagic disease of newborn occur in infancy, viz. early-HDN, classic-HDN and late-HDN.

Early HDN :

These infants have severe and often life-threatening haemorrhage at the time of delivery or during the first 24 hours after birth.

Although idiopathic cases have been reported (Anthony, 1961 and Wilson, 1972), the early-HDN is typically seen in infants whose mothers have taken drugs that affect vitamin K metabolism. Maternal anticonvulsants have also been linked to early-HDN (Mountain et al, 1970; Bleyer, Skinner, 1976; Deblay et al, 1982 and McNinch et al, 1983).

Early-HDN is seen in those cases whose mothers use therapeutic doses of warfarin (an anticoagulant) during pregnancy (Stevenson et al, 1980).

Extent of bleeding varies from skin bruising (Mountain et al, 1970) to umbilical bleeding (Mountain et al, 1970 and McNinch et al, 1983) to wide spread and fatal intracranial, intrathoracic, intraabdominal and gastrointestinal haemorrhage (Bleyer Skinner, 1976, and Deblay et al, 1982).

Classic-HDN

Classic-HDN typically occurs at 2 to 5 days

of age (Sutherland et al, 1967, Aballi, 1974 and McNinch et al, 1983).

Sutherland et al (1967) reported that the incidence of classic-HDN prior to the initiation of routine vitamin K prophylaxis varied widely but observed that it could be as high as 1.7% in full term infants. Authors further reported that the incidence of moderate to severe bleeding among breast fed infants, who had not received vitamin K was 15 to 20 times higher than in those who had received cows milk or vitamin 'K' or both.

McNinch et al (1983) observed that affected children developed generalized ecchymoses or gastro-intestinal tract bleeding. They documented that intra-cranial haemorrhage was less common in classic-HDN.

Late-HDN

Haemorrhage occurring one week after post natal life is considered as late-HDN.

Rapaport (1946) reported 7 infants of hypoprothrombinemia secondary to chronic diarrhoea.

Matsusaka et al (1981) observed that most of the later-HDN infants had acute intracranial haemorrhage which could be intracerebral, intracerebellar, subarachnoid, subdural or epidural. They further documented that many of these infants died, and those who survived frequently had severe neurologic sequele. Vitamin K deficiency was the leading cause of haemorrhage in

infants, after the first week of life.

Nagi et al (1982) reported that the second most common feature of late haemorrhagic disease was widespread deep ecchymoses or nodular purpura.

VIEWS REGARDING PARENTERAL OR ORAL SUPPLEMENTATION OF VITAMIN K

Brinkhouse et al (1937) documented low prothe rombin levels in normal newborn infants. Others viz. Waddell et al and Nygaard et al (1939) demonstrated that these low levels could be elevated by the administration of vitamin K.

Dam et al (1937) differentiated haemorrhagic disease of the newborn from bleeding, secondary to other causes.

Holt and McIntosh (1939) recommended that all the infants should be promptly given 0.5 mg vitamin K_1 orally at birth.

Aballi et al (1957; 1959) studied coagulation factors in newborns and observed that factor II, VII, IX and X were reduced in the newborns as compared to levels in adults.

The nutrition committee of the American Academy of Pediatrics recommended in 1961, that prophylactic administration of vitamin 'K' be given to all newborn infants.

Aballi and de Lamerens (1962) differentiated haemorrhagic disease of the newborn from bleeding, secondary to other causes.

Welfering (1962) observed that coagulation factors II, VII, IX and X were reduced in newborns as indicated by Thrombotest. He concluded that the test was abnormal when any one or all factors mentioned above were reduced. He opined that in some newborn infants, coagulation deficiency at birth was so great as to constitute a risk of haemorrhage, which could be prevented by administering vitamin 'K' to the mothers 4-24 hours prior to delivery. However, some infants did not show much lowering of coagulability and therefore haemorrhage could be prevented by giving vitamin 'K' orally or parenterally (I/M) just after birth.

Godman and Deposito (1966) reported five patients with bleeding disorder with hypoprothrombinaemia that occurred after neonatal period.

Mountain et al (1970) suggested that anticonvulsant therapy during pregnancy, especially treatment with barbiturates, caused coagulation defects. They suggested that if vitamin 'K' (especially K_1) was given to mother near term then there would be no bleeding tendencies in her newborn infant.

Bleyer et al (1976) documented that anticonvulsant therapy during pregnancy i.e. phenobarbitone and

phenytoin sodium caused coagulation defects which could result in bleeding during the early neonatal period.

Van Doorm et al (1977) claimed that haemorrhagic disease of the newborn was due to vitamin 'K' deficiency and developed at 2-4 days of post-natal life. Authors suggested that if haemorrhagic disease of newborn could be prevented by administration of vitamin 'K' then generalised bleeding tendencies in the newborns should be uncommon. Authors also suggested that substitution therapy should be given to high risk infants. They also suggested that it would be a backward step to stop routine prophylaxis with vitamin K.

Hope et al (1982) in their study on three cases of alpha-1-antitrypsin deficiency observed haemorrhagic tendency in them which responded to vitamin K. In their study they stressed that the patients were all breast fed and none had received vitamin K at birth. Because of their presentation with bleeding disorder, they were all initially diagnosed as having haemorrhagic disease of newborn. However, their presentation was not of classical type of neonatal haemorrhage. All of them had conjugated hyperbilirubinaemia in the first few months of life associated with raised transaminase (consistent with neonatal hepatitis) and the clotting disorder was due to lack of vitamin K dependent factors. Authors opined that greater awareness of early features of haemorrhagic disease

of newborn may lead to early diagnosis of the condition. They also suggested that PI(protease inhibitor) phenotyping should always be considered in cases of haemorrhagic disease in early life, especially if associated with raised hepatic enzymes.

Vimenez et al (1982) observed that in one month old infants vitamin K dependent clotting factors, prothrombin time (PT) and partial thromboplastin time (PTT) were similar whether they were breast or bottle fed. However, the Normotest (NT) and Thrombotest (TT) were slightly prolonged in breast fed group. They observed that these values were also higher in breast fed infants as compared to the adult values. They stressed that the higher values could be associated with infection, especially diarrhoea and following antibiotic therapy.

Debley et al (1982) documented that if vitamin K_1 20 mg was given orally daily for two days to a mother, taking antiepileptic drugs, then transplacental transportation of vitamin K occurred and prevented bleeding tendencies in the newborn. They suggested that vitamin K_1 prophylaxis should be a routine for epileptic mothers near term.

Dunn (1982) stressed that there is a need to accept the wise consel given by Holt and McIntosh in 1939 that all infants should be promptly given 0.5 mg of vitamin K_1 orally at birth. He documented that as all

paediatricians appreciate , vitamin K_1 was well and rapidly absorbed when given orally. There was, however, a need for the commercial availability of vitamin K_1 Powders of 0.5-1.0 mg strength to avoid the expensive practice of using sterile ampoules for oral use. He stressed that the widespread demand of such preparation should make its marketing profitable.

Shirahata et al (1982) noted that 7-10 days after the intramuscular injection of vitamin K coagulation values declined in breast fed infants. But they were unable to determine the normal dose and proportion of its absorption from the gut.

McNinch et al (1983) observed that if vitamin K prophylactically was not given to breast fed babies the problem of haemorrhagic disease of newborn (HDN) became more common. This problem of HDN could prove fatal if not recognised and treated promptly. They also suggested that selective policy of giving vitamin K_1 prophylactically only to babies, considered at risk was no longer adequate and that vitamin K_1 should be given to every newborn baby.

Verity et al (1983) treated four infants of intracranial haemorrhage secondary to vitamin K deficiency. Three of these infants were noted to have received 1 mg vitamin K at birth. They studied the blood clotting abnormalities and found highly raised prothrombin

time, activated partial thromboplastin time (APTT) and thrombin time (TT). They noted that these abnormal clotting tests reversed to normal, after administering a further dose of vitamin K. They found that these abnormalities were due to deficiency of vitamin K and therefore, concluded that more than 1 mg of vitamin K_1 should be given at the time of birth.

Ware and Mills (1983) suggested that vitamin K should probably be given to all newborn babies and certainly to those who would receive breast feeding.

McKenna et al (1983) studied the effects of warfarin sodium (an anticoagulant) taken by lactating mothers. They claimed that despite easily detectable warfarin values in the plasma of these mothers, none could be identified in their milk. They observed that infants born to these mothers had prolonged prothrombin time but not as long as those mothers themselves : although, warfarin per se was not detected in the plasma of infants. Recommendation by the authors was that mothers receiving warfarin sodium be allowed to breast feed their infants. Authors, however, cautioned that there was a need to establish similar information with regard to other infrequently administered anticoagulants.

Lane et al (1983) opined that a decision to withhold vitamin K prophylaxis was ill advised. They suggested that clinicians should remain alert to the possibility of vitamin K deficient haemorrhage in older

Chaou et al (1984) observed that the prophylactic injection of vitamin K at the time of birth was not a routine procedure in Taiwan. Authors had not seen delayed haemorrhage in any baby born at their hospital.

Nagao and Nakayama (1984) commented on a case report of Lane et al (1983), regarding intracranial haemorrhage in a normal infant who had vitamin K deficiency. Lane et al (1983) had argued against the tendency to stop routine prophylaxis of vitamin K at birth. Authors, while supporting the opinion of routine prophylaxis felt that cases of intracranial haemorrhage (due to idiopathic vitamin K deficiency) found in Japan could be related to the abandonment of routine vitamin K administration at birth. Authors suggest that vitamin K_1 given at birth may not resolve all the problem of idiopathic vitamin K deficiency, but most of it could be. prevented.

Aballi (1985) observed that alpha-1 antitrypsin deficiency could actually resulted in inadequate vitamin K absorption consequently low vitamin K in breast milk was unable to compensate for the defective absorption if it was there owing to cholestatic liver disease, alpha-1-antitrypsin deficiency or antibiotic therapy.

Lane et al (1985) observed that exclusively breast fed babies had prolonged prothrombin time and a 15-20 times greater risk of bleeding as compared to those who were given cow's milk or vitamin 'K' or both.

Kries et al (1985) observed that in late onset of HDN some other factors must be involved. One possibility was malabsorption of vitamin K, perhaps due to intraluminal bile salt deficiency.

Motohara et al (1985) suggested that PIVKA-II level might be more useful than a coagulation test, since low activity of vitamin K dependent coagulation factors some time reflect impaired production of these factors (due to immaturity rather than vitamin K deficiency. The level of PIVKA-II (protein, induced by vitamin K absence) or antagonistic II was raised in the state of vitamin K deficiency and was normal after administration of vitamin K. Authors depicted the mechanism of PIVKA-II as follows :

PIVKA-II ---Vitamin K--- Prothrombin
|
(Prothrombin Precursor)

Authors observed that lack of data on PIVKA-II levels in cord blood in newborn was the cause of vitamin K prophylaxis controversy. The level of PIVKA-II was measured by ELISA technique using a monoclonal antibody.

According to McNinch et al (1985) vitamin K does not cross the placenta easily. Its concentration

maternal value and the mean concentration of vitamin K dependent factors (II, VII, IX and X) were only 30-60% of the normal adult values. 500 ml breast milk contains 0.5 - 3 ugm vitamin K_1 while 500 ml of bottle feed would yield approximately 1.5 - 4.5 ugm of vitamin K_1. "Since the majority of breast fed infants did not develop haemorrhagic disease, the daily intake necessary for protection of those at risk must be extremely small", opined the authors. Commenting on the storage and dispensing of vitamin K, authors wrote that since 1.0 mg vitamin K was given orally and keeping in view the economy and simplicity we should use solution of 10 mg/ml (stored in amber coloured bottles) and these could be supplied in the cord care packs.

Sann et al (1985) documented that if oral vitamin K (2 mg) was given, normal or high serum vitamin K concentration could be achieved by the end of first week of life. However, it was not known whether this dose was sufficient to maintain normal serum K values and normal coagulation activities later on.

Kries et al (1985) observed that latent vitamin K deficiency without clinical evidence of bleeding could be more common than reports suggest. It was more common in Asia than in Japan. Authors documented that low oral intake and feeding of maternal milk, known to contain little vitamin K, accounted for the high PIVKA-II

K content of maternal milk was lower than that in formula, vitamin K deficiency beyond the 4th week was observed in only one out of 113 breast fed babies. For this, authors provided two explanations - one was that breast fed infants beyond the 4th week of life received more milk because lactation was by then fully established,, secondly, vitamin K absorption was mature.

Garrow et al (1986) measured thrombo test value in 72 healthy full term babies. They observed that breast fed babies from birth until 2 days after showed a pronounced drop in thrombo test value which was prevented by one intramuscular injection of 1.0 mg vitamin K. They agreed with the view expressed by American Academy of Pediatric (1961) that vitamin K should be given to all newborn infants.

Connor et al (1986) documented that oral vitamin K was equally effective as compared to intramuscular vitamin K. They studied 37 infants born at home and 19 infants born in the hospital. Amongst home delivered newborns, 18 were randomly selected to receive no vitamin K (Group A) and 19 received 2 mg vitamin K (group B). Among the hospital delivered babies 18 received 1 mg vitamin K intramuscularly (group C) and remaining infants received 0.5 mg vitamin K intramuscularly. The prothrombin time of babies in group A was significantly longer than that of group B and C at 3rd day of life. But no difference in the prothrombin time was found between group B and C after 3

days. Authors suggested that routine administration of an oral preparation of vitamin K at timely intervals during the first year of life would eliminate or decrease this potential fatal disorder.

Shapiro et al (1986) were of the opinion that in order to prevent late idiopathic haemorrhagic disease associated with breast feeding, all the newborn infants be given vitamin K as soon as possible after birth.

Motohara et al (1987) documented that PIVKA-II was the most sensitive test to find out the status of vitamin in the serum of infants. They documented that oral prophylaxis was more economical and simpler than intramuscular prophylaxis. They suggested that oral route was most practical when the administration was required for all newborn infants.

Tripp and McNinch (1987) documented that for reasons of acceptability to parents, safety, convenience and cost they used 1 mg oral dose of vitamin K_1 for routine prophylaxis in infants at special risk from HDN (those born prematurely or admitted to the special care baby unit or babies born to mothers taking anticonvulsants). They have suggested that in consideration of the absorption factor, which may be hampered due to some reasons, one should use more oral dose of vitamin K.

Marwaha et al (1987) documented that vitamin K deficiency must be suspected in a bleeding neonate or

disease.

Narang (1989) documented that inspite of so many controversies one should adopt the routine prophylaxis of all high risk infants. He also suggested that the recommendation should be enlarged so that all babies who would be on breast feeds should receive vitamin K prophylaxis.

Merchant et al (1989) observed that human neonate had sub-optimal stores of vitamin K at birth due to inadequate placental transfer and poor storage capacity. They have documented that early HDN (within 24 hours) caused mucosal and skin bleeds while late HDN caused bleeding in intestine and CNS. It has been suggested by the authors, that partial supplementation of diet with one or two formula feeds would be protecting against vitamin K deficiency.

Sen et al (1989) suggested that efficacy of oral vitamin in high risk infants should be evaluated. They suggested that oral vitamin K was equally effective as intramuscular vitamin K prophylaxis.

Mathur et al (1990) suggested that prophylaxis had usually been reserved for babies considered especially at risk for HDN. They have documented that there was no need to give vitamin K to full term healthy babies, but it should be given in all cases like difficult delivery and all preterm infants.

MATERIAL AND METHODS

MATERIAL AND METHODS

The present study was conducted in the department of Paediatrics, M.L.B. Medical College and Hospital, Jhansi from June, 1990 to May, 1991 to observe the efficacy of oral vitamin 'K' intake on the prothrombin time of newborn babies.

SELECTION OF CASES

The study was conducted on 51 full term babies (gestational age more than 37 weeks), weighing more than 2 kg and who were born after uncomplicated vaginal delivery. All the babies had normal APGAR score at the time of birth (1 minute APGAR score).

Babies were selected from the labour room of the department of Obstetrics and Gynaecology. The selection of cases was random. Babies were randomly assigned to 4 different groups viz., A, B, C and D.

1. Group A consisted of 10 babies who received 1 mg vitamin K intramuscularly.
2. Group B consisted of 8 babies who received 0.5 mg vitamin K intramuscularly.
3. Group C consisted of 18 babies who received 1 mg vitamin K orally.
4. Group C consisted of 15 babies who did not receive vitamin K at all.

All the babies who were selected for present

study were exclusively breast fed. Informed consent was obtained from the mothers for prior administration of vitamin K and subsequently blood sample was collected between 36-72 hours of vitamin K administration.

ANTENATAL HISTORY

Full antenatal history was elicited and selected babies belonged to mothers who were not having following history or complications during pregnancy viz. :

1. Toxaemia of pregnancy.
2. Fever (with or without a rash) during the first trimester of pregnancy.
3. Syphilis, hepatitis, heart disease, severe anaemia, Herpes infection during pregnancy.
4. Drug intake like antiepileptics during pregnancy.

All babies were examined in the labour room and all those who were the outcome of complicated delivery, had birth anoxia or showed congenital anomalies were excluded from the present study.

MATERIAL USED

1. Commercially prepared thromboplastin capsule.
2. Normal saline (0.9% solution of sodium chloride).
3. Marked test tube and pippette.
4. Solution of calcium chloride (M/40 solution of calcium chloride).
5. Stop watch.

COLLECTION OF SAMPLE

First of all 0.2 ml solution of 3.1% trisodium citrate was poured in a marked test tube, then Child's part was prepared to collect venous blood sample. The blood (1.8 ml) was directly collected in the marked test tube containing trisodium citrate solution (0.2 ml).

Then plasma was separated from the venous blood after centrifuging the blood and the plasma, thus, separated was transferred to another test tube.

PRINCIPLE OF PROTHROMBIN TIME

Principle of the test is based on a fact that if all the substances theoretically required for coagulation of blood, are mixed in optimal amount then the prothrombin time is directly proportional to the concentration of prothrombin present. The test is customary called prothrombin time (PT).

Depending upon the exact proceudre, two methods of prothrombin time determination are known (a) Giegy's method, (b) Quicke's one stage method.

Quicke's one stage method was used in the present study to determine prothrombin time.

PROCEDURE FOR QUICKE'S ONE STAGE METHOD

In this procedure first of all thromboplastin solution (6.5% suspension) was prepared in normal saline. The main steps of the test are :

1. Contents of 1 capsule of thromboplastin were dissolved in 5 ml normal saline and 2 ml of supernatant from this solution was transferred to another test tube. To this 2 ml solution (supernatant) was added 2 ml calcium chloride (M/40 solution of calcium chloride) and the solution containing mixture was incubated for 15 minutes at 37°C.
2. Venous blood of the case (1.8 ml) was taken in another test tube containing trisodium citrate(0.2ml). This was centrifuged for 2 minutes to separate plasma and then incubated for 5 minutes at 37°C.
3. Finally 0.2 ml solution was taken from the mixture of thromboplastin and calcium chloride in another test tube and to that was added 0.1 ml of baby's plasma, while the stop watch was started. Time taken to form a web in the test tube was noted and the reading was taken as prothrombin time (PT) in seconds. With each batch of test a control was run.

All the tests were performed within one hour after taking the venous blood from the babies selected for the study.

Each test was performed twice and mean of the two readings was taken as prothrombin time (PT) in seconds.

OBSERVATIONS

OBSERVATIONS

Present study was conducted in department of Pediatrics, M.L.B. Medical College and Hospital, Jhansi, from June, 1990 to May, 1991 to assess the efficacy of oral vitamin 'K' in neonates.

Fifty one neonates were selected for the study and were assigned to four groups viz. A, B, C and D. Prothrombin time of all the study cases was determined in 31 batches. A control case was taken with each batch of tests. Healthy adults were taken as control. cases.

DISTRIBUTION OF BABIES

1. Group A included 10 babies.
2. Group B included 8 babies.
3. Group C consisted of 18 babies and
4. Group D comprised of 15 babies.

As shown in Fig. 1, (total 51 cases were selected for the study. Out of them 10(19.68%) cases belonged to group A, 8(15.68%) cases belonged to group B, 18(35.28%) and 15(29.40%) babies belonged to group C and D respectively.

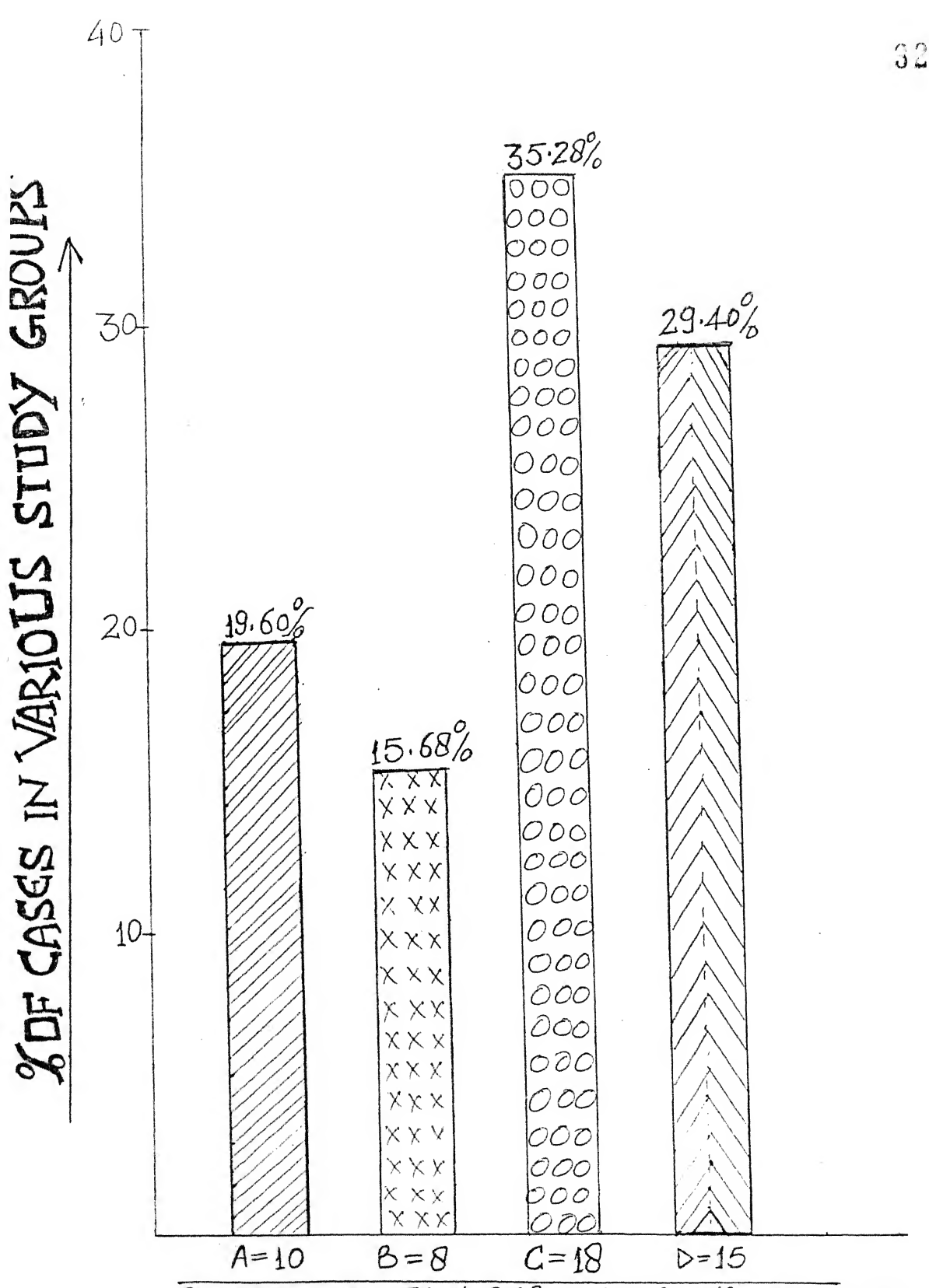

40
30
20
10
% OF CASES IN VARIOUS STUDY GROUPS
19.60%
15.68%
35.28%
29.40%
A=10
B=8
C=18
D=15
BOTTOM OF EACH BAR SHOWS NO. OF CASES IN VARIOUS STUDY GROUPS

Fig. I

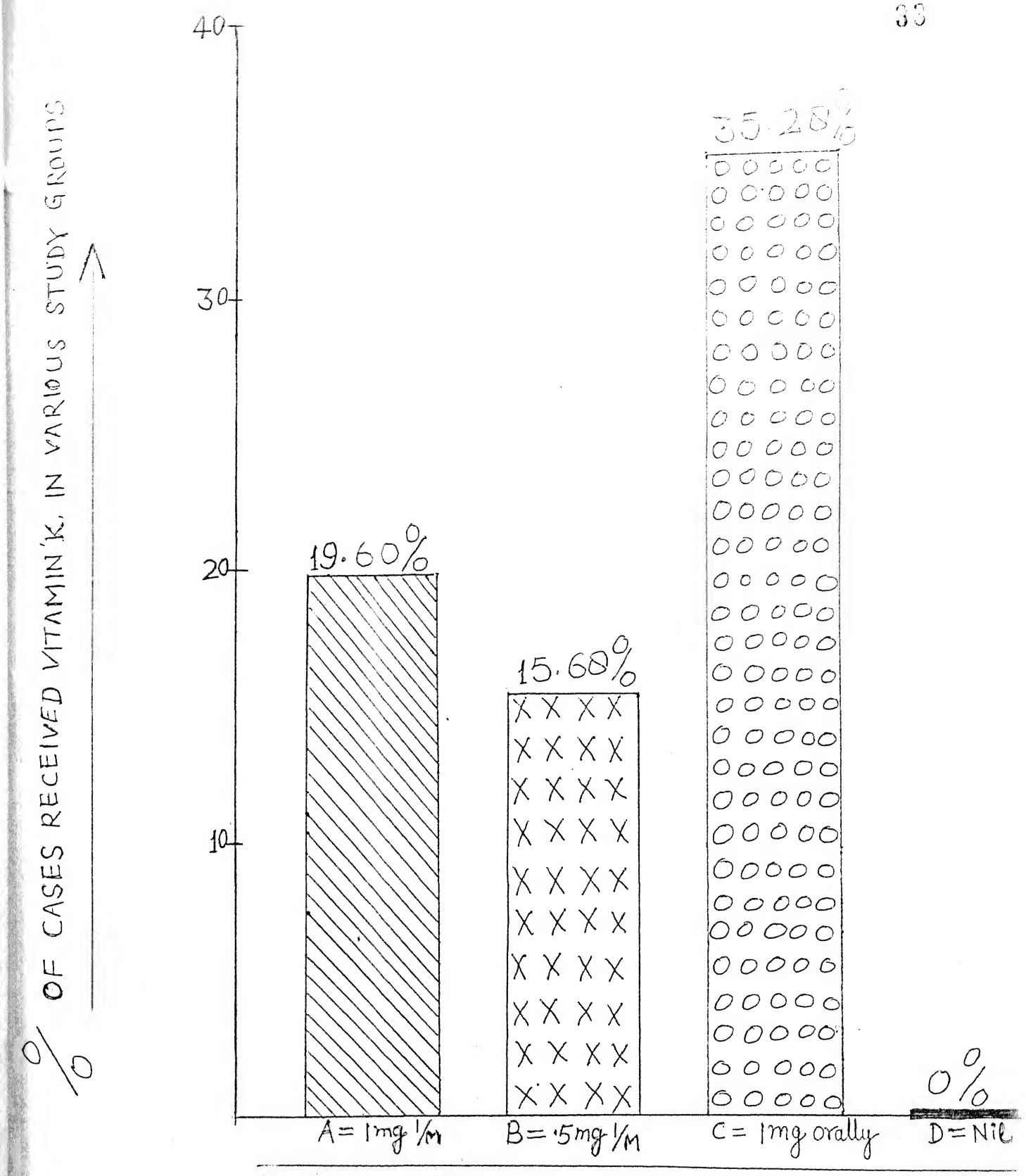

40
30
20
10
% OF CASES RECEIVED VITAMIN 'K' IN VARIOUS STUDY GROUPS
19.60%
15.68%
35.28%
0%
A= 1mg I/M
B= .5mg I/M
C= 1mg orally
D= Nil
EACH BOTTOM SHOWS STUDY GROUP & MODE OF VITAMIN "K" ADMINISTRATION

Fig. II

TABLE I

Mode of administration of vitamin K in each study group.

Study group	No.of cases	Mode of administration
A	10	1 mg Intramuscularly
B	8	0.5 mg Intramuscularly
C	18	1 mg orally
D	15	Not given

Table I shows that cases of group A received 1 mg of vitamin K intramuscularly while babies of group B received 0.5 mg vitamin K intramuscularly. Babies of group C received 1 mg of vitamin K orally and the babies of group D did not receive any vitamin K.

Table II shows the mean birth weight of different study groups. Mean birth weight of babies of group A was 2.72±0.18 kg, while that of group B babies was 2.85±0.19 kg. The mean birth weight of babies of group C and D was 2.62±0.19 and 2.74±0.22 kg respectively.

TABLE II

Mean birth weight of babies in various study groups.

Study group	No. of cases	Birth weight (Mean±S.D.) (kg)	Range (kg)
A	10	2.72 ± 0.18	2.5 - 3.0
B	8	2.85 ± 0.19	2.6 - 3.2
C	18	2.62 ± 0.19	2.2 - 3.0
D	15	2.74 ± 0.22	2.3 - 3.00

Table III shows that the mean birth weights of babies of various study groups were almost identical and the differences were not statistically significant.

TABLE III

Statistical analysis showing significance of the difference of mean birth weight among various study groups.

Groups	p values			
	A	B	C	D
D	70.5	70.1	70.05	-
C	70.2	70.1	-	-
B	70.1	-	-	-
A	-	-	-	-

p 70.05 : Not significant
p 70.5 : Not significant
p 70.1 : Not significant

Table IV shows the sex distribution of cases in various study groups.

1. In the study group A total cases were 10 and out of these 5(50%) were male and the remaining 5(50%) female.
2. In group B, out of a total of 8 cases, 6(75%) were males and rest 2(25%) were females.

3. In group C, 9(50%) out of 18 cases were males and 9(50%) cases females.

4. In group D, out of total 15 cases, 7(46.65%) were male and 8(53.35%) were females.

TABLE IV

Sex distribution of cases in various study groups.

Study groups	No.of cases	Male		Female	
		No.of cases	Perce-ntage	No.of cases	Perce-ntage
A	10	5	50.00	5	50.00
B	8	6	75.00	2	25.00
C	18	9	50.00	9	50.00
D	15	7	46.65	8	53.35

TABLE V

Mean age at which the samples for prothrombin time were collected in various study groups.

Study groups £ £ £	No.of cases	Age(Hours) (Mean ± S.D.)
A	10	49.13 ± 13.03
B	8	48.03 ± 15.13
C	18	48.00 ± 14.14
D	15	48.00 ± 14.14

TABLE VI

Statistical analysis showing significance of the difference of mean ages among various study groups.

	p values			
Groups	A	B	C	D
D	70.5	70.5	70.5	7 -
C	70.5	70.5	-	-
B	70.5	-	-	-
A	-	-	-	-

p 70.5 : Not significant.

Tables V and VI show the mean age of cases of various groups at the time of sampling of the venous blood. Mean ages at which the samples were collected in different groups of cases were almost idential and the differences between them were not statistically significant.

TABLE VII

Prothrombin time in seconds in various groups.

Study groups	No.of cases	Prothrombin time (Second) Mean ± S.D.	Range
A	10	19.24 ± 3.32	14.0 - 26.2
B	8	19.17 ± 3.14	12.0 - 22.0
C	18	20.13 ± 3.31	13.0 - 26.0
D	15	34.10 ± 4.02	27.4 - 40.8

TABLE VIII

Batch No.	No.of study cases tested	Prothrombin time in each control case(Seconds)
1	2	16.0
2	1	15.0
3	2	16.5
4	1	18.0
5	2	18.0
6	1	18.0
7	2	18.0
8	1	18.0
9	1	16.2
10	1	16.0
11	2	14.0
12	3	14.0
13	1	14.0
14	2	14.0
15	3	13.8
16	2	15.2
17	2	14.2
18	1	16.0
19	1	15.0
20	1	13.8
21	1	13.0
22	4	15.2
23	4	16.0
24	1	16.0
25	2	14.2
26	1	14.8
27	1	14.8
28	2	14.8
29	1	16.0
30.	1	12.8
31	1	14.0

N = 31

Mean$\pm$S.D.= 15.33$\pm$1.49

Table VII shows that the prothrombin time values in study groups A, B, and C were almost identical while the value of prothrombin time in group D was elevated as compared to study groups A, B and C.

The mean prothrombin time of control cases was 15.33±1.49 seconds as showin in table VIII.

TABLE IX

Statistical analysis showing significance of the difference in prothrombin time among various groups.

Groups	p values			
	A	B	C	D
D	<0.001*	<0.001*	<0.001*	-
C	>0.1	>0.2	-	-
B	>0.5	-	-	-
A	-	-	-	-

* p <0.001 : Highly significant
p >0.1 : Not significant
p >0.2 : Not significant
p >0.5 : Not significant

DISTRIBUTION OF PROTHROMBIN TIME VALUES IN VARIOUS STUDY GROUPS —

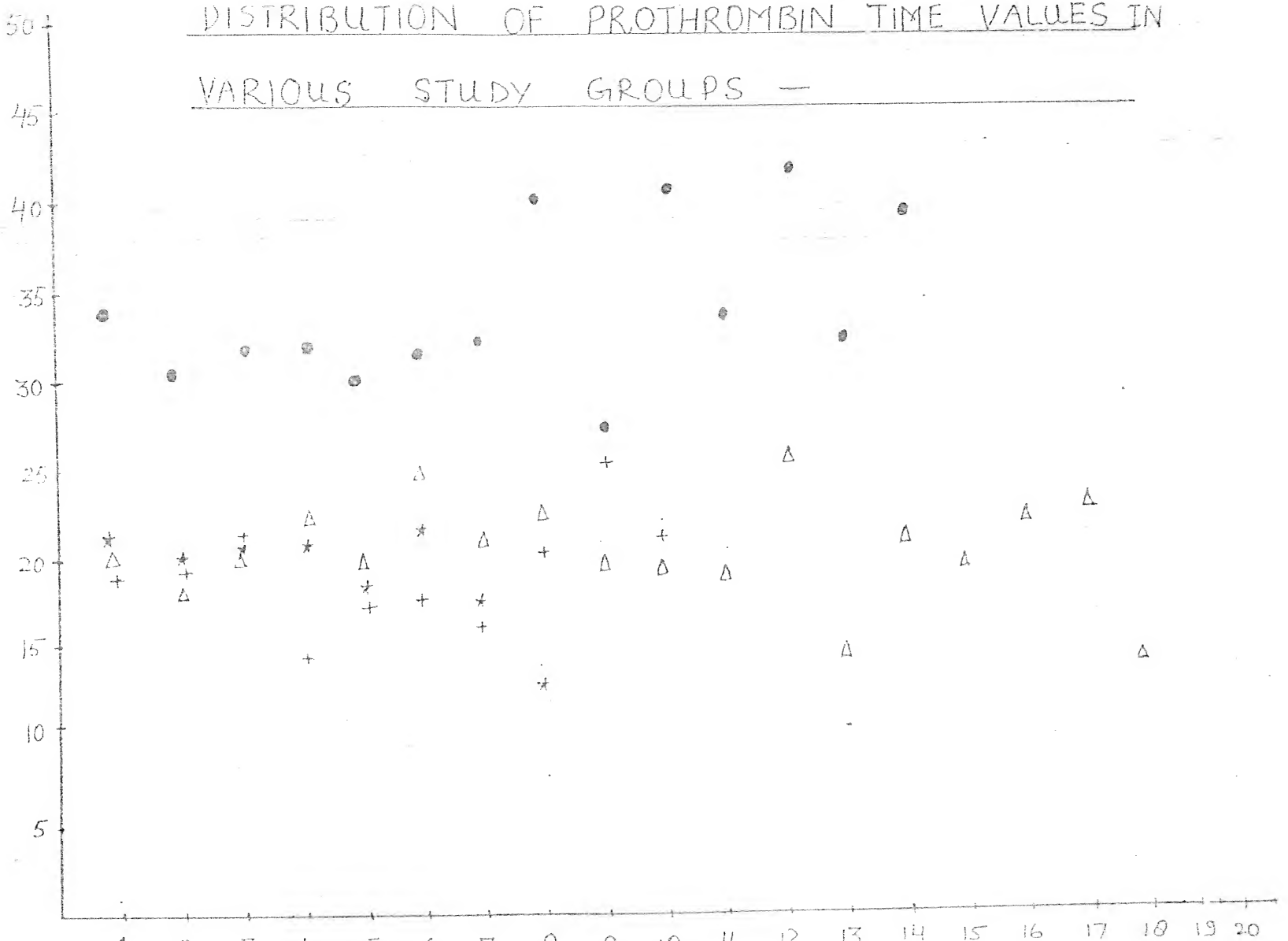


FIG- III

GROUPS
- D = ● (15) DID NOT RECEIVE VITAMIN K AT ALL
- C = Δ (18) RECEIVED 1 mg VITAMIN K ORALLY
- B = * (8) RECEIVED 0.5 mg VITAMIN K I/M
- A = + (10) RECEIVED 1 mg VITAMIN K I/M

Table IX shows that the prothrombin time values in group A, B and C were nearly identical and differed significantly from that of group D ($p < 0.001$) where the values were markedly raised. Prothrombin times values in group A, B and C were almost identical and were not raised as compared to adult control cases.

D I S C U S S I O N

DISCUSSION

The present study was conducted to observe the effect of oral versus parenteral vitamin K intake on the prothrombin time of newborn babies. The study was conducted on 51 full term babies (gestational age more than 37 weeks) weighing more than 2 kg and who were born after uncomplicated vaginal delivery. All the babies had normal APGAR score at the time of birth (one minute APGAR score).

In the past, many studies have been conducted to evaluate the role of vitamin K to prevent the haemorrhagic disorder in the newborn infants but most of these were conducted to evaluate the efficacy of parenteral vitamin K.

Mean activity of vitamin K dependent coagulation factors in the newborn is about 50% of adult values. This falls to half to one third of its initial activity by the second or third day especially in breast fed babies (Oski and Naiman, 1972). Medical literature contains numerous challenges to the recommendation that all newborn babies receive prophylactic vitamin K at birth. These workers have suggested that defective coagulation in the newborns was not because of vitamin K deficiency, but owing to the liver immaturity (Van Doorm et al and Gobel et al, 1977 and Malia et al, 1980). Van Doorm et all failed to find vitamin K deficiency in cord blood.

Malia et al (1980) studied 24 cord blood samples and found no evidence of vitamin K deficiency after he had done several different assays. Gobel et al (1977) studied 154 healthy infants at 72-94 hours of age who had not received vitamin K at birth and they did not find depressed prothrombin level in any infant. All the infants in Gobel's series had received feeding during the first 24 hours of age and none was exclusively breast fed. Weight of evidence today, however, does show that vitamin K deficiency is in fact responsible for defective coagulation (Corrigan and Kryo, 1980). Yoshioka et al (1982) found depressed prothrombin levels in 6 out of 8 term infants at 3 days of age.

The present study was planned to evaluate the role of oral water soluble vitamin K in the haemorrhagic disease of newborn babies. Since a water soluble preparation of vitamin K_1 was not available, the synthetic water soluble vitamin K analogue (Menadione sodium disulphite) was used instead, which is the same form of drug that is being used by parenteral route. This form of vitamin K has a possible advantage that it is water soluble and is easily absorbed, even in the absence of bile salts (Shearer et al, 1974). In moderate doses water soluble vitamin K is quite safe but large doses may cause, hemolysis and jaundice (Aballi et al, 1962).

In the present study, all the 51 cases selected were absolutely breast fed. Breast feeding has been

implicated as a necessary factor in the pathogenesis of haemorrhagic disease of the newborn (Sutherland et al, 1967). Vitamin K is approximately four times more concentrated in cow's milk than in breast milk (Dam et al, 1942).

All the 51 cases were randomly alloted to four different groups viz., A, B, C and D. Parenteral 1 mg vitamin K was given to the cases of study group A,; 0.5 mg parenteral vitamin K was administered to study group B; oral 1 mg vitamin K was given to the cases of study group C while no vitamin K was given to the cases of study group D. Vitamin K was administered within 2 hours after birth. O'Connor and Addiego (1986) studied 41 full term infants and arranged them in three groups A, B and C. No vitamin K was given to the cases of study group A, 2 mg water soluble vitamin K_1 (Phytonadione) was given to the cases of study group B and 1 mg vitamin K_1 was given to the cases of study group C. Vitamin K was given within 2 hours after birth. In another study by Sen et al (1989), 120 full term infants who were delivered by uncomplicated vaginal delivery and were arranged in four different groups A, B, C and D. Cases of study group A were given 1 mg vitamin K (Menadione sodium bisulphite) intramuscularly, cases of group B were given 0.5 mg vitamin K (Menadione sodium bisulphite) intramuscularly, cases of study group C were given 1 mg vitamin K (Menadione sodium bisulphite) orally while no vitamin K was given to the cases of

group D. Vitamin K was administered within 2hours after birth.

In the present study mean birth weight of babies in the four study groups A, B, C and D was 2.72±0.18, 2.85±0.19, 2.62±0.19, and 2.74±0.22 kg respectively. Birth weight differences among the four study groups were not statistically significant.

In the present study the sex distribution (M : F) in four study groups A, B, C and C was 1 : 1, 3 : 1, 1 : 1, and 1: 1.1 respectively.

In the present study the mean ages at which the blood samples for prothrombin time were collected in the four study groups A, B, C and D were 49.13± 13.03, 48.03±15.13, 48±14.14 and 48 ±14.14 hours respectively. The difference between mean age was not statistically significant. In a study conducted by Sen et al (1989) the mean ages at which the sample for prothrombin time were collected in the four study groups A, B, C and D were 48±13.14, 49.33±13.23, 47.9±13.4 and 47.27±10.66 hours respectively. Study done by O'Connor and Addeigo (1986) does not gave any table to depict mean ages of collecting blood samples but the authors have mentioned that samples were collected on the 3 day of birth.

The routine mode of vitamin K administration to the newborn babies has been the injection of 1 mg

of vitamin K intramuscularly. In the present study vitamin K was given intramuscularly as well as orally. None the cases who received oral vitamin K had hemolysis and/or jaundice, none was observed to have vomiting. Sen et al (1989) used the synthetic analogue (Menadione sodium bisulphite) of vitamin K orally as well as parenterally while O'Connor and Addiego (1986) used the water soluble vitamin K_1 both orally and intramuscularly.

The present study showed that the prothrombin time (which is a good measure of blood coagulation factors II, vII, IX and X) of babies in group A, B, and C (19.24±3.32, 19.17±3.14 and 20.13±3.31 seconds respectively) was almost identical , showing that 1 mg of vitamin K orally was just as effective as 1 mg or 0.5 mg vitamin K given intramuscularly. It was also seen that group D babies who did not receive vitamin K had a marked prolongation of prothrombin time (34.10± 4.02 seconds). The prothrombin time of group D babies was significantly prolonged ($p < 0.001$) as compared to prothrombin time observed in group A, B and C babies. On an average prothrombin time of group D babies was prolonged 2½ times as compared to other groups who had received vitamin K_1 either orally or parenterally. Thus group D infants who had not received any vitamin K were at risk to develop hemorrhagic disease.

Sen et al (1989) reported prothrombin time values in study group A (who received 1 mg vitamin K intramuscularly) 17.1±2.68, in group B (who received 0.5 mg vitamin K intramuscularly) 17.2±4.42, and in group C (who received 1 mg vitamin K orally) 17.0±2.36 seconds respectively. These values were almost idential and differed significantly ($p < 0.001$) from that of group D (who did not receive vitamin K at all) being was 33.1±12.20 seconds). These findings are almost similar to those observed in the present study.

O'Connor and Addiego (1986) reported the following prothrombin time values in their study groups A, B and C: Prothrombin time values in study group B (who received 2 mg water soluble vitamin K_1 orally) - 9.83±0.56 seconds; Prothrombin time in study group C (who received 1 mg vitamin K_1 intramuscularly) - 10.33± 1.20 seconds. Thus the prothrombin time values in study group B and C were almost identical and difference was not statistically significant. Prothrombin time in study group A (who did not receive vitamin K), the values were raised, being 12.33±3.42 seconds. The prolonged time in group A cases was statistically significant ($p < 0.01$) when compared to group B and group C babies.

SUMMARY AND CONCLUSION

SUMMARY AND CONCLUSION

The present study was conducted in the department of Pediatrics, M.L.B. Medical College, and Hospital, Jhansi from June, 1990 to May, 1991 to assess the efficacy of oral water soluble vitamin K in neonates.

The study was conducted on 51 full term babies (gestational age more than 37 weeks) weighing more than 2 kg and who were born after uncomplicated vaginal delivery. The selection of cases was random and cases were randomly assigned to four different groups viz. A, B, C and D. The study was done in 31 batches and with each batch of tests a healthy adult was run as control case. All the babies who were selected for the study were exclusively breast fed.

A full antenatal history was taken prior to selection of cases. The mean birth weight of babies of group A was 2.72 ± 0.18 kg, while that of group B babies was 2.85 ± 0.19 kg. The mean birth weight of babies in group C and D was 2.62 ± 0.19 and 2.74 ± 0.22 kg respectively.

The sex distribution (M : F) in study groups A, B, C and D was 1 : 1, 3:1, 1 : 1 and 1 : 1.1 respectively. Vitamin K was administered to cases in study group A, B and C within two hours after birth. The mean age of blood sample collection in study group A, B, C and D was 49.13±13.03, 48.03±15.13, 48.00±14.14 and 48.00±14.14 hours respectively. None of the cases had any complication after administration of vitamin K.

After collecting the sample prothrombin time was determined within one hour by Quick's one stage method. The mean prothrombin time of cases in the study group A, B, and C was 19.24±3.32, 19.17±3.14 and 20.13± 3.31 seconds respectively, being almost identical. Prothrombin time of cases in the study group D was prolonged (34.10±4.02 seconds) as compared to adult control cases. The mean prothrombin time of adult control cases was 15.33±1.49 seconds. The prolonged mean prothrombin time in study group D was statistically significant ($p < 0.001$) as compared to control cases while the prothrombin time values in study groups

A, B, and C were not significantly different from control cases.

From the present study, it is concluded that :

1. Vitamin K prophylaxis may be given to all the newborn infants.
2. With an advantage oral water soluble vitamin K can safely be given to newborns as prophylaxis.
3. Oral water soluble vitamin K is as effective as intramuscular vitamin K.
4. 1 mg oral water soluble vitamin K is as effective as 1 mg or 0.5 mg of intramuscular vitamin K.
5. Oral water soluble vitamin K is a much simpler form of prophylaxis and avoids intramuscular injection.

B I B L I O G R A P H Y

BIBLIOGRAPHY

1. Aballi AJ, de Lamerens S : Coagulation changes in neonatal period and in early infancy. Pediatr Clin North Am 1962; 9 : 785.

2. Aballi AJ, Howard CE, Triplett RF : Absorption of vitamin K from the colon in the newborn infant. J Pediatr 1966; 68 : 305.

3. Aballi AJ : Haemorrhagic disease of the newborn. Pediatr Ann 1974; 3(2) : 35.

4. Aballi AJ : Vitamin K deficiency in newborn. (Letter). Lancet 1977; 2 : 559.

5. Aballi AJ : Vitamin K and the newborn (Letter). Lancet 1978; i : 1358.

6. Aballi AJ : Vitamin K deficiency. Pediatrics 1985; 75 : 372-3.

7. American Academy of Pediatrics : Report of committee on nutrition, vitamin K compounds and the water soluble analogues. Use in therapy and prophylaxis in pediatrics. Pediatr 1961; 4 : 281-337.

8. Anonymous : Vitamin K and newborn (Editorial). Lancet 1978; i : 755-7.

9. Atkinson PM, Bradlow BA, Moulineaux JD et al : Acarboxyprothrombin in cord plasma from normal neonates. J Pediatr Gasteroenterol Nutr 1984; 3 : 540-53.

10. Barness LA : Vitamin K deficiency : Beherman RE, Vaughan VC eds. Nelson text book of Pediatrics, 13th ed. Philadelphia : W.B. Saunders, 1987, p. 154.

11. Bhanchet P, Tuchinda S, Kathirat P et al : A bleeding syndrome in infants due to acquired prothrombin complex deficiency. Clin Pediatr 1977; 16 : 992.

12. Biggs R, Human blood coagulation, hemostasis, and thrombosis. Oxford : Blackwell Scientific publications, 1972.

13. Bloch CA, Rothberg AD, Bradlow BA : Mother infant prothrombin precursor status at birth. J Pediatr Gastroenterol Nutr 1984; 3 : 101-3.

14. Brinkhous KM, Smith HP, Warner ED : Plasma prothrombin level in normal infancy and in hemorrhagic disease of the newborn. Am J Med Sci 1937; 193 : 475.

15. Caballero FM, Buchanan GR : Abetalipoproteinemia presenting as severe vitamin K deficiency. Pediatrics 1980; 65 : 161.

16. Caffey J : The whiplash shaken infant syndrome. Pediatr 1974; 54 : 396.

17. Chaou WT, Chaou ML, Eitzman DV : Intracranial hemorrhage and vitamin K deficiency in early infancy. J Pediatr, 1984; 105 : 880-4.

18. Committee on Nutrition : American Academy of Pediatrics : Vitamin K_1 compounds and water soluble analogues, use in therapy and prophylaxis in

pediatrics. Pediatrics, 1961; 28 : 501-07.

19. Corrigan JJ, Earnest D : Factor II antigen in liver disease and warfarin induced vitamin K deficiency. Am J Hematol, 1980; 8 : 249.

20. Corrigan JJ, Kryo JJ : Factor II (Prothrombin) levels in cord blood. Correlation of coagulant activity with immunoreactive protein. J Pediatr 1980; 97 : 979-83.

21. Corrigan JJ : Vitamin K dependent proteins. Adv Pediatr 1981; 28 : 57-70.

22. Dacie JU, Lewis SM : Practical hematology, Edinburgh Churchil Livingstone, 1984; pp 216-8.

23. Dam H : Cholesterinstoffwechsel in huhnereiern und huhnchen. Biochem Zeitschr 1929; 215 : 415.

24. Dam H, Dyggve H, Larsen H et al : The relation of vitamin K deficiency to hemorrhagic disease of the newborn. Adv Pediatr 1952; 5 : 129.

25. Dam H, Glavind J, Larsen EH et al : Investigations into the causes of the physiological hypoprothrombinemia in newborn children. The vitamin K content in women's milk and cow's milk. Acta Med Scand, 1942; 112 : 210.

26. Dabley MF, Vert P, Andre M et al : Transplacental vitamin K prevents hemorrhagic disease of infant of epileptic mother. Lancet 1982; 1 : 1247.

27. Deshpande SA, Marwaha RK, Garewal G et al : Clinico hematological and sonographic profile of late

haemorrhagic disease due to vitamin K deficiency. Paper presented at the annual conference of Indian Academy of Pediatrics, Jodhpur, 1988.

28. Dunn PM : Vitamin K_1 for all newborn babies(Letter). Lancet 1982; ii : 770.

29. Edson JR : Vitamin K deficiency in newborn (Letter). Lancet 1977; ii : 187.

30. Frick PG, Reidler G, Brogly H : Dose response and minimal daily requirement of vitamin K in man. J Appl Physiol, 1957; 23 : 387.

31. Garrow D, Chisholm M and Radford M : Vitamin K and thrombo test values in full term infants. Arch Dis Child 1986; 61 : 349-51.

32. Gellis SS, Lyon RA : The influence of the diet of the newborn infant on the prothrombin infex. J Pediatrics 1941; 19 : 495.

33. Gobel U, Rosenow SS, Petrich C et al : Vitamin K defieiency in newborn (Letter). Lancet 1977; ii : 187-88.

34. Goldman HI, Diposito F : Hypoprothrombinemic bleeding in young infants. Am J Dis Child 1966; 111 : 430.

35. Haroon Y, Shearer MJ, Rahim S. et al : The content of phylloquinone (vitamin K_1) in human milk, cow's milk and infant formula foods determined by high performance liquid chromatography J Nutr, 1982; 112:1105-17.

36. Harper HA : The fat soluble vitamins : Harper HA, Rodwell VW, Mayes PA eds. Review of physiological chemistry, 16th ed. Los Altos, California : Lange, 1977, p. 154.

37. Hathway WE : New insights on vitamin K. Hematol Oncol Clin North Amer 1987; 1 : 367-79.

38. Hope PL, Hall MA, Willward-Suddler GH et al : Alpha-1-antitrypsin deficiency presenting as a bleeding diathesis in the newborn. Arch Dis Child 1982;57: 68-79.

39. Ishii E, Ueda K : Thrombo test values and effect of vitamin K administration for infants. Arch Dis Child 1987; 62 : 540-541.

40. Jimenez R, Navarrete M, Jimenez E et al : Vitamin K dependent clotting factors in normal breast fed infants. J Pediatr 1982; 100 : 424-6.

41. Keenan WJ, Jewett T, Glueck HI : Role of feeding and vitamin K in hypoprothrombinemia of the newborn. Am J Dis Child 1971; 121 : 271-7.

42. Keith DA, Gallop PM : Phenytoin, hemorrhage, skeletal defects and vitamin K in the newborn. Med Hypotheses 1979; 5 : 1347.

43. Kries RV, Shearer MJ, Gobel U : Vitamin K in infancy. Eur J Pediatr, 1988; 147 : 106-12.

44. Kries RV, Maase B, Becker A et al : Latent vitamin K deficiency in healthy infants. Lancet, December 21/28, 1985.

45. Lane PA, Hathway WE, Githens JH et al : Fatal intracranial hemorrhage in a normal infant secondary to vitamin K deficiency. Pediatrics, 1983; 72 :562-4.

46. Lane PA, Hathway WE : Vitamin K in infancy. J Pediatrics, 1985; 106 : 351-9.

47. Leclercq M, Crozet M, Durand J et al : Determination of phylloquinone (vit. K_1) in sera of newborn and and adults by high performance liquid chromatography. In Frigerio A ed : Chromatography in Biochemistry, medicine and environmental research. Armsterdam, Elsevier Scientific publication 1983, p. 235-47.

48. Lehmann J, : Vitamin K as a prophylactic in 13000 infants. Lancet, 1944; i : 493-4.

49. Leibman HA, Furie BC, Furié B : Hepatic vitamin K dependent carboxylation of blood clotting proteins. Hepatology 1978; 2 : 488-492.

50. Lovric VA, Jones RF : Hemorrhagic syndrome of early childhood. Aust Ann Med 1967; 16 : 173.

51. Malia RG, Preston FE, Mitchel VE : Evidence against vitamin K deficiency in normal neonate. Thromb Haemot 1980; 44 : 159-60.

52. Marwaha RK, Kumar A, Garewala G et al : Vitamin K deficiency related bleeding manifestations in older neonates and infants. Indian Pediatr,1987;24:307.

53. Mathur GP, Mathur S, Goenka R et al : Prothrombin time in first week of life with special reference to vitamin K administration, Indian Pediatrics, 1990; 27 : 723-25.

54. Mc Carthy PT, Shearer MJ, Gau G : Vitamin K content of human liver at different ages. Haemostasis 1986; Suppl 5 : 84-5.

55. McKenna R, Cole RE, Vasan U : Is warfarin sodium is contraindicated in lactating mother. J Pediatr 1983; 103 : 325-7.

56. McNinch AW, Orme RL, Trip JH : Haemorrhagic disease of the newborn returns. Lancet 1983; i : 1089-90.

57. McNinch AW, Upton C, Samuels M et al : Plasma concentrations after oral or intramuscular vitamin K_1 in neonates. Arch Dis Child 1985; 60 : 814-8.

58. Merchant RH, Divekar RM : Late haemorrhagic disease with intracranial haemorrhage. Indian Pediatrics 1988; 25 : 381-84.

59. Merchant RH ; Divekar R, Shah MD : Late haemorrhagic disease of infancy. Indian Pediatr 1989; 26 : 553-7.

60. Meyer T, Angus J : The effect of large doses of 'Synkavit' in the newborn. Arch Dis Child 1956; 31 : 212-5.

61. Mori PG, Bhisogni C, Odino S'et al : Vitamin K deficiency in the newborn. Lancet 1977; ii:138.

62. Motohara K, Matsukura M, Nishiyama S et al : Vitamin K deficiency in young infants. Studies on prophylactic vitamin K administration and its pathogenesis. Japanese J Pediatric Society, 1983; 87 : 1650-6.

63. Motohara K, Matsukura M, Matsuda I et al : Severe vitamin K deficiency in breast fed infants. J Pediatrics 1984; 105 : 943-45.

64. Motohara K, Kuroki Y, Kam H et al : Detection of vitamin K deficiency by use of ELISA for circulating abnormal prothrombin. Pediatrics Res 1985;19:354-7.

65. Motohara K, Endo F, Matsuda I : Effect of vitamin K administration on Acarboxyprothrombin (PIVKA-II) levels in newborn. Lancet Aug 1985; ii : 242-4.

66. Motohara K, Endo F and Matsuda I : Screening for late neonatal vitamin K deficiency by acarboxyprothrombin in dried blood spot. Arch Dis Child 1987;62:370-75.

67. Nagao T : Vitamin K deficiency in infancy in Japan (Letter). Pediatr 1984; 74 : 315-6.

68. Nakayama K : The etiology of vitamin K deficiency in infants. Perinatal Medicine 1982; 12 : 1029-34.

69. Narang N : Haemorrhagic disease of the newborn. Indian Pediatr 1989; 26 : 523-4.

70. Nygaard KK : Prophylactic and curative effect of vitamin K in haemorrhagic disease of newborn. Acta Obstet Gynaecol Scand, 1939; 19 : 361.

71. O'Connor ME, Livingstone DS, Hannah J et al : Vitamin K deficiency and breast feeding. Am J Dis Child 1983; 137 : 601-2.

72. O'Connor ME, Addiego JE : Use of oral vitamin K to prevent hemorrhagic disease of newborn infant. J Pediatri 1986; 108 : 616-19.

73. Oski FA, Naiman JL : Hematologic problems in newborns. Philadelphia WB Saunders 1972; pp 250-57.

74. Oslon RE : The function and metabolism of vitamin K. Ann Rev Nutr 1984; 4 : 281-37

75. Rapaport S, Dodd K : Hypoprothrombinemia in infants with diarrhoea. Am J Dis Child 1946; 71 : 611.

76. Rosenthal P, Leibman MM, Thaler MM : Letter, Alpha-1-antitrypsin deficiency and severe infantile liver disease. Am J Dis Child 1979; 113 : 1195-96.

77. Sann L, Leclercq M, Gillaumont M et al : Serum vitamin K concentration after oral administration of vitamin K in low birth weight infants. J Pediatr, 1985; 107 : 608-11.

78. Sann L, Leclercq M, Tronchy J et al : Serum vitamin K_1 concentration and vitamin K dependent clotting factor activity in maternal and fetal cord blood. Am J Obst Gyn 1985; 153 : 771-4.

79. Sen S, Kumari S, Narayan S et al : Efficacy of oral water soluble vitamin K in neonates a controlled prospective study. Paper presented in the Annual Conference of Indian Academy of Pediatrics at Jodhpur, 1988.

80. Sen S, Kumari S, Narayan S et al : Efficacy of oral water soluble vitamin K in neonates. Indian Pediatr 1989; 26 : 992-5.

81. Shapiro AD, Jacobson LJ, Armon ME et al : Vitamin K deficiency in the newborn infant. Prevalence and perinatal risk factors. J Pediatrics 1986;109:675-80.

82. Shearer MJ, Mallinson CN, Webster GR : Absorption and excretion of an oral dose of tritiated vitamin K in man. Br. J Haematology 1970; 22 : 579-88.

83. Shearer MJ, McBurney A, Barkhan P : Studies on absorption and metabolism of phyloquinone(Vitamin K_1) in man. Vitam Horm 1974; 16 : 992-8.

84. Shearer MJ, Rahim S, Barkhan P et al : Plasma vitamin K_1 in mothers and their newborn babies. Lancet 1982; ii : 460-3.

85. Shirahata A, Najiri T, Horinchi T et al : Normotest screenings and prophylactic oral administration for idiopathic vitamin K deficiency in infancy. Acta Hematol Japan, 1982; 4 : 203.

86. Stenflow J, Fernlund P, Egan W et al : Vitamin K dependent modifications of glutamic acid residues in prothrombin. Proc Natl Sci USA 1974; 71 : 2730.

87. Sutherland JM, Glueck HI, Gleser G : Hemorrhagic disease of the newborn. Breast feeding as a necessary factor in the pathogenesis. Am J Dis Child 1967; 113 : 524-33.

88. Sutor AH, Pancochar H, Neiderhoff H et al : Vitamin K deficiency haemorrhage in four entirely breast fed infants. aged 4-6 weeks(German) Dtsch Med Wochenschr 1983; 108 : 1635.

89. Tay JSH, Tip WCL : Vitamin K dependent clotting factors in normal breast fed infants (Letter). J Pediatr, 1982; 101 : 795.

90. Townsend DW : The haemorrhagic disease of the newborn. Arch Pediatr 1894; 11 : 559.

91. Tripp JH, McNinch AW : Haemorrhagic disease and vitamin K. Arch Dis Child 1987; 62 : 436-7.

92. Van Doorm JM, Muller AD, Hemkar HC : Vitamin K deficiency in newborn. Lancet 1977; ii : 708-9.

93. Van Doorm JM, Muller AD, Hemkar HC : Heparin like inhibitor, not vitamin K deficiency in the newborn. Lancet 1977; ii : 852-3.

94. Verity CM, Carswell F, Scott GL : Vitamin K deficiency causing infantile intracranial haemorrhage after neonatal period. Lancet 1983;i : 1439.

95. Von Kries R, Reifenhauser A, Gobel U et al : Late onset haemorrhagic disease of newborn with temporary malabsorption of vitamin K_1. Lancet 1985;i:1035.

96. Waddell WW, Guerry D : The role of vitamin K in the etiology, prevention and treatment of haemorrhage in the newborn infant. J Pediatr 1939; 15 : 802.

97. Ware S, Mills M : Vitamin K deficiency causing infantile intracranial haemorrhage after the neonatal period. Lancet 1983; i : 1439-40.

98. Wefring KW : Hemorrhage in the newborn and vitamin K prophylaxis. J Pediatrics 1962; 61 : 686-92.

99. Whitfield MF, Salfield SAW : Accidental administration of syntometrine in adult doses to the newborn. Arch Dis Child 1980; 55 : 68-70.

100. Yoshioka K, Kinoshita S, Takamiya O et al : Abnormal antigens of factor II, VII and IX in newborns and breast fed infants with vitamin K deficiency. Acta Haematol Japan 1982; 45 : 860.
